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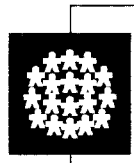

Puget Sound
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March 15, 2000

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Dockets Management Branch (HFA-305) 00 P 160 '00 MAR 29 A10 :45
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 99D-5046: Draft Guidance for Industry; Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

To Whom it May Concern:

Please accept these comments to the January 2000 version of the above draft Guidance. As described in the Introduction, the document is an extension of the FDA's thinking on the July 24, 1997, Federal Register announcing revision to 21 CFR 601.12, Changes to an Approved Application. The impetus for this CFR revision was to **harmonize regulation** and **reduce the reporting burden**. We support these objectives.

The preamble to the Final Rule defines the factors used to determine whether a change is likely to have adverse effect and the extent of that risk. Included in these factors are the level of knowledge about the product and its active components, the type of change being implemented, and the likelihood that adverse effect would be detected. The type of product is also to be considered where small changes may introduce large risks which are difficult to measure in the final product. To this end, the FDA avoided exhaustive definition of major, moderate, and minor changes yet conveyed the intent behind the Rule. We agree with the FDA's factors to be used for determining risk and effect.

We also support the FDA's emphasis on quality systems with the belief that the licensed establishment bears the responsibility for appropriate change control, internal monitoring, and management oversight. This is in harmony with ISO 9000, Medical Device Quality Systems, Recommendations for Quality Assurance in Blood Establishments, and industry standards. The new pilot program for licensing irradiated blood products furthers this approach. With this responsibility lies the need to exercise control over the implementation.

Most of the changes in a blood establishment are not conducted in isolation. The modifications are highly interrelated—rarely does a donor questionnaire change without modifications to SOP or criteria for acceptance. When new computer systems are implemented, often procedures for quarantine, discard, labeling, or distribution require revision. These are complex matters requiring robust project management at the establishment level. In this regard, we submit the following:

Harmonization: *Is it?*
The interpretation provided in the Draft Guidance document of 21 CFR 601.12, Changes to an Approved Application, hobble a blood establishment's ability to effectively manage changes. Contrary to other harmonization efforts undertaken by the FDA, the draft Guidance appears to situate the FDA to determine the adequacy, effectiveness, and suitability of each change. Was this the intention of the FDA to insert an approval step for nearly every modification a blood establishment may attempt? How does this conform with the stated objective to harmonize when this approach is a polar opposite to the guidance applied in other FDA regulated fields and the direction being introduced with pilot licensure programs?

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Applicability: *When does this Guidance apply?*
It is virtually impossible to ferret out change which is subject to reporting due to a license being in place and that which is exempt. The regulation provides for establishments maintaining an approved Biologics License Application (BLA) to notify the FDA according to the potential for risk to the safety, purity, potency, or effectiveness of the product. It must be emphasized that this regulation was intended only for instances where an approved application exists (i.e., a license).

This concept is lost in the draft Guidance document as the scope of the language encompasses virtually every function in a blood establishment. One does not separately maintain a license for donor suitability determination, quarantine, or recordkeeping, for example. There is no longer a separate Establishment License to cover general issues of facilities, validation, quality systems. Does the FDA intend for reporting of virtually every change itemized in the guidance if the establishment is at all licensed? For example, if a Red Blood Cell license is the only licensed product and a change is made in the unlicensed irradiation procedures, must the establishment submit a preapproval submission (PAS) simply because it has a license? 21 CFR 601.12, Changes to an Approved Application, very clearly defines when a modification is subject to reporting, however the examples provided in the draft Guidance muddy the lines.

Extent: *Why would the FDA need to approve changes which are more restrictive than regulation or guidance?*
On December 14, 1997, during public comment on the initial draft Guidance document, CBER representatives adamantly denied that changes more restrictive than those previously approved would require any form of advance FDA approval. Submission in the Annual Report would be satisfactory, if it were believed that any potential for adverse impact existed. The draft Guidance contradicts the logical interpretation provided at that meeting.

The draft Guidance exhaustively describes examples of what the FDA believes to evoke reporting despite the fact that the establishment may not believe the change to in any way *adversely* impact safety or efficacy. These changes are commonly due to current developments in scientific literature, CDC guidance, or manufacturer revisions. Very real examples include the suitability criteria for intranasal cocaine use or the extension of malaria deferral periods for armed services in certain areas of Korea. To encumber these revisions designed to maintain the current levels of safety with a lengthy PAS application subject to review cycles of one year (or more) jeopardizes the safety of the blood supply and interferes with the Medical Director's capacity to judiciously determine donor suitability.

Blood is a fully characterized biologic: *Why require any form of advance approval, particularly when guidance exists?*
The draft Guidance strays significantly from risk factors provided in the Final Rule. Blood components are fully defined products in the CFR. The level of knowledge about the product, its active components, and the nature of changes introducing risk are well understood. According to the criteria for determining if advance approval should be applied, one would think that these factors would diminish the FDA's concern that permission to institute the change is necessary. Yet the list of items requiring either a PAS or 30 days' advance notice (CBE30) is voluminous for even well-characterized modifications for which existing guidance addresses the controls to be instituted. Examples include donor suitability determinations, High Risk questions, quarantine and disposition of unsuitable products, request for use of an alternative procedure where guidance is available. It is reasonable that the FDA receive notification of such changes, particularly if these items are part of an approved license, however, to require any form of preapproval is contrary to the preamble in the Final Rule.

Focus: *The emphasis seems not to be on risk, but on the "what" of the change...*
Unfortunately, the draft Guidance focuses on the method or means of implementing the change instead of directing the concern towards the *potential* for adverse effect. The draft Guidance identifies changes in SOPs or forms rather than identifying changes to controls established to ensure safety. Instead of identifying the donor history form as a target for PAS or CBE30, the intent of the regulation would be furthered by requiring the manufacturer to conduct a determination as to the risk introduced, precautions in place, and the potential impacts of the proposed change. The question should be: "How is the process being affected?", rather than, "What tangibles in the process are being modified?" Based on an adequate internal hazard analysis, the manufacturer should then be compelled to notify the FDA in accordance with the Final Rule.

Annual Report: *Duplication and added reporting burdens!*
With respect to the Annual Report, the Draft Guidance compounds the volume of reporting to be performed by a blood establishment. Already a Form 2830 must be submitted to CBER annually for every registered establishment. This document identifies the type of establishment, products collected, manufactured, and distributed, and is signed by the authorized official. If harmonization is sought, discontinue the requirement that blood establishments register annually. Duplication of this information in the Annual Report defies the stated purpose to streamline reporting.

Additionally, the particular information requested in the Annual Report does not approximate even remotely what could be construed as a risk to safety. The addition of instrumentation already FDA-cleared and approved as part of the establishment's license represents what type of hazard? Clearly the institution must apply quality systems and assure appropriate controls, but the Annual Report itself has no bearing on whether or not this occurs. According to the draft Guidance, the sole purpose behind the Annual Report is to verify that the institution has reported changes in the proper category. Requiring that every change in the establishment be reported to CBER is not an expeditious way to make this determination for either the FDA or the blood center.

Timeliness: *Are these submissions subject to managed review cycles? If so, can we afford to wait a year?*
Based on the Puget Sound Blood Center's experience, FDA approval for changes is not routinely obtained in a timely fashion. The approval for a variance for electronic crossmatch was nearly one year with multiple SOP revisions required to satisfy the FDA. These revisions were not structural in nature. Labeling improvements which eliminated handwritten information—an obvious source for error—have been held up for months due to the fact that they differ from the guidelines published in 1985. Product codes are not approved unless they match exactly those published by a trade organization (AABB) despite the fact that implementation of the AABB codes would cause deleterious inventory effects within our institution.

These are very real examples of system changes which have stalled under current FDA approval schemes. Given the extended list of changes subject to Preapproval and CBE30 by the draft Guidance, this situation will likely be worsened. FDA approval of each and every change will constitute the critical path for any significant implementation.

Recommendation
It is our recommendation that the Draft Guidance be modified such that the establishment determines the extent of the risk and the severity of the outcomes and reports to CBER based on this assessment. The reports would be in accordance with 21 CFR 601.12, Changes to an Approved Application. The

responsibility for conducting a hazard assessment and mitigating risk rests with the establishment. All reference to specific forms being revised or general references to changes in procedures or processes should be deleted. Additionally, the Annual Report should be preserved for providing the FDA information which is useful and truly represents items with a potential for introducing risk.

As the draft Guidance stands, it no longer reflects the intent described in the July 24, 1997, Federal Register announcing revision to 21 CFR 601.12, Changes to an Approved Application. The end result is an increase in the reporting burden, stymied attempts to maintain a safe blood supply, and the introduction of further dissonance rather than harmonization of regulation.

Should the FDA finalize the approach represented in the draft Guidance document, inconsistencies and inaccuracies must be addressed. Namely, the use of "and", as well as "or", in the use of published FDA guidance documents for SOP revisions, definition of what a "post-approval" inspection is, clarification that these items only apply to an approved application, and item A)2)—why would one need a plasma license in order to collect plasma as a byproduct? The definitions obtained from the reverse side of the form 2830 do not provide substantial benefit to the document. Additionally, should the FDA advocate the use of a specific Uniform Donor History form, as the draft Guidance implies, this form should be subject to public comment. This is particularly true since the FDA seems to be using this document as a litmus test for any blood establishment's submission relating to donor interviews.

Also, the PAS must be subject to some form of managed review cycle with faster turnaround times. Each of these changes must be assigned a tracking number and given priority according to the nature of the change. An entire computer system implementation could be resting with the FDA's review of a change to the donor questionnaire. An expectation for a timely response is reasonable.

Sincerely,

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Director, Quality Assurance/Regulatory Affairs

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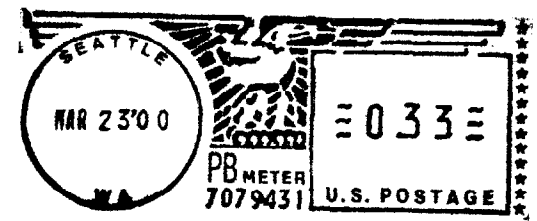

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